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Preparation of 2-Magnesiated 1,3,5-Triazines via an Iodine−Magnesium Exchange

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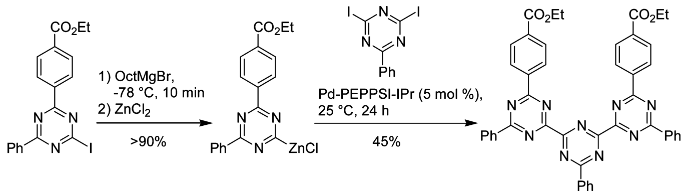
ABSTRACT



Functionalized iodo- and diiodo-1,3,5-triazine derivatives readily undergo an I/Mg exchange with BuMgCl, *s*BuMgCl, or OctMgBr at low temperatures furnishing 2-magnesiated and 2-zincated 1,3,5-triazines (after transmetalation with $ZnCl_2$). This method also offers a convenient access to dimagnesiated triazines. Furthermore, it allows the preparation of functionalized 1,3,5-triazinyl dimers and trimers, interesting for their opto-electronic properties.

Heterocycles have gained increased significance in modern chemistry.[1] Among N-containing heterocycles, 1,3,5-triazine derivatives[2,3] have found numerous industrial applications as pharmaceuticals,[4] liquid crystals,[5] reactive dyes,[6] and organic light-emitting diodes (OLEDs).[7] However, the efficient syntheses of polyfunctional 1,3,5-triazines, including dimeric and trimeric triazine derivatives, remain a synthetic challenge. Metalated heterocyclic intermediates have proven to possess great potential for the concise synthesis of functionalized heterocycles.[8] Especially polyfunctionalized organomagnesium compounds show a high tolerance toward a wide range of functional groups and are easily accessible, e.g., via Br/Mg or I/Mg exchange reaction.[9] It has been reported that the reactions of 2-chloro-4,6-dimethoxy-1,3,5-triazine with ketones using lithium powder and substoichiometric amounts of naphthalene involving a lithiated 1,3,5-triazine intermediate afford the corresponding alcohols in 13−50% yield.[10] Herein, we report a straightforward and

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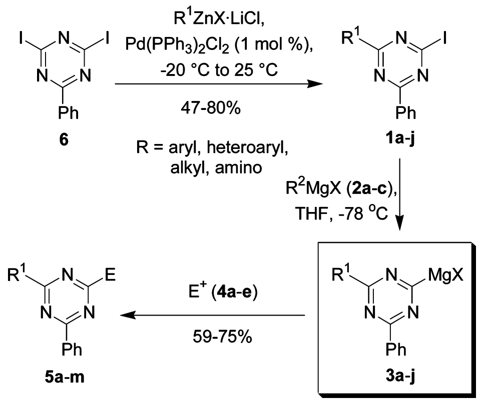
practical preparation of fully substituted 1,3,5-triazines via magnesiated triazines as well as synthetic routes to highly functionalized 1,3,5-triazine dimers and trimers which are expected to be valuable advanced materials. Thus, various functionalized iodotriazine derivatives of type **1** underwent a smooth I/Mg exchange reaction using BuMgCl (**2a**) or OctMgBr (**2b**; 1.1 equiv, −78 °C, 10 min) affording the corresponding 2-magnesiated 1,3,5-triazines of type **3** (Scheme 1).

Scheme 1. Preparation of Functionalized 1,3,5-Triazinylmagnesium Reagents of Type **3** and Functionalization with Various Electrophiles



Subsequent reactions of the triazinylmagnesium reagents **3** with various electrophiles (E^+; **4a**−**e**) led to substituted triazines of type **5** in 59−75% yield (Scheme 1 and Table 1).

In comparison to well-established Hal/Mg exchange reagents such as *i*PrMgCl,[11] the Grignard reagents BuMgCl (**2a**) and OctMgBr (**2b**) are less nucleophilic and more selective, avoiding undesired substitution products. The substrates for the exchange reactions, namely, the iodotriazine derivatives of type **1**, were prepared from 2,4-diiodo-6-phenyl-1,3,5-triazine[12] (**6**) using Negishi-type cross-couplings[13] with functionalized organozinc reagents in the presence of $Pd(PPh_3)_2Cl_2$ (1 mol %) in 47−80% yield (Scheme 1).

The reaction of 6-iodo-4-octyl-2-phenyl-1,3,5-triazine (**1a**) with BuMgCl (**2a**; 1.1 equiv, −78 °C, 10 min) provided the corresponding triazinylmagnesium chloride (**3a**), which after transmetalation with $ZnBr_2$·LiCl (1.1 equiv, −20 °C, 30 min) undergoes a cross-coupling with ethyl 4-iodobenzoate (**4a**) in the presence of $Pd(dba)_2$ (5 mol %) and tfp[14] (= $P(2\text{-furyl})_3$; 10 mol %), affording the trisubstituted 1,3,5-triazine derivative **5a** in 62% yield (entry 1, Table 1). Additionally, a copper-catalyzed allylation[15] (CuCN•2LiCl, 20 mol %) of **3a** with ethyl (2-bromomethyl)acrylate[16] (**4b**) produced the acrylate **5b** in 73% yield (entry 2). In the same manner, a range of 1,3,5-triazinylmagnesium reagents bearing electron-donating functional groups such as a 2-thienyl group (**3b**), a diphenylamino group (**3c**), or an aryl group bearing various substituents (**3d**−**j**) were prepared by reaction with BuMgCl (**2a**) or OctMgBr (**2b**; 1.1 equiv, −78 °C, 10 min) with 2-iodo-1,3,5-triazine derivatives (**1a**−**j**). The resulting 1,3,5-triazinylmagnesium reagents **3b**−**j** reacted with various electrophiles **4b**−**e** affording the fully substituted 1,3,5-triazines **5c**−**m** in 59−75% yield (entries 3−13). Thus, a Cu(I)-catalyzed allylation (CuCN•2LiCl, 20 mol %) of the magnesiated triazine **3b** with ethyl 2-(bromomethyl)acrylate[16] (**4b**) furnished the trisubstituted acrylate **5c** in 59% yield (entry 3). Similarly, the magnesium reagent **3c** afforded, after a Cu(I)-mediated benzoylation with **4c** (CuCN•2LiCl, 1.1 equiv), the triazinyl ketone **5d** in 71% yield (entry 4). Moreover, the substituted 2-triazinyl alcohol **5e** was obtained after addition of the organomagnesium reagent **3d** to PhCHO (**4d**) in 61% yield (entry 5). Remarkably, also electron-poor triazines **1e**,**f** underwent a smooth I/Mg-exchange with BuMgCl (**2a**; 1.1 equiv, −78 °C, 10 min) affording the functionalized 1,3,5-triazinylmagnesium reagents **3e**,**f**. Subsequent Cu(I)-catalyzed allylation (CuCN•2LiCl, 20 mol %) with ethyl 2-(bromomethyl)acrylate[16] (**4b**) or addition to PhCHO (**4d**) afforded the trisubstituted 1,3,5-triazines **5f** and **5g** in 54−71% yield (entries 6 and 7). The 1,3,5-triazine-based Grignard reagents **3g**−**j** bearing electron-withdrawing functional groups such as ester, cyano, and halo groups in the *ortho*- or *para*-position of the phenyl substituent were prepared via a rapid I/Mg exchange with OctMgBr (**2b**; 1.1 equiv, −78 °C, 10 min) from the corresponding substituted 2-iodo-1,3,5-triazines **1g**−**j**. In comparison to BuMgCl (**2a**), OctMgBr (**2b**) avoids side products due to a nucleophilic substitution of the triazine ring. Thus, the 1,3,5-triazinylmagnesium

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(12) Obtained after treatment of 2,4-dichloro-6-phenyl-1,3,5-triazine with HI. See: (a) Vlád, G.; Horváth, I. T. *J. Org. Chem.* **2002**, *67*, 6550. (b) Supporting Information.

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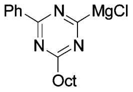
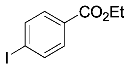
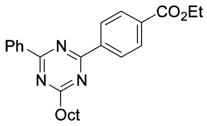
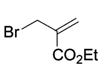
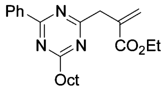
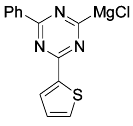
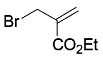
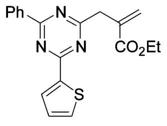
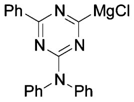
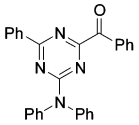
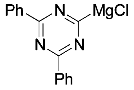
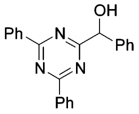
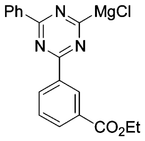
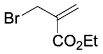
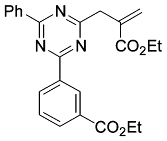
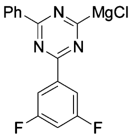
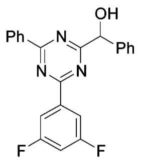
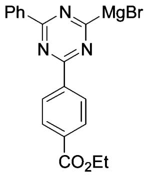
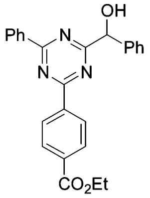
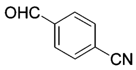
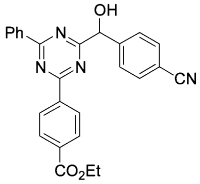
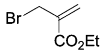
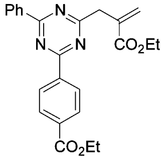
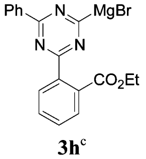
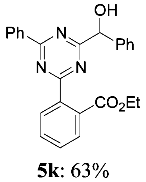
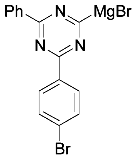
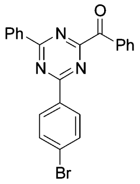
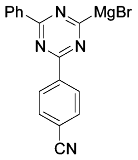
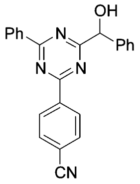
Table 1. Functionalized 1,3,5-Triazine Derivatives of Type **5** Obtained by I/Mg Exchange and Subsequent Quenching with an Electrophile

entry	magnesium reagent	electrophile	product, yield[a]
1	 **3a**[b]	 **4a**	 **5a**: 62%[d]
2	**3a**[b]	 **4b**	 **5b**: 73%[e]
3	 **3b**[b]	 **4b**	 **5c**: 59%[e]
4	 **3c**[b]	PhCOCl **4c**	 **5d**: 71%[f]
5	 **3d**[b]	PhCHO **4d**	 **5e**: 61%
6	 **3e**[b]	 **4b**	 **5f**: 71%[e]
7	 **3f**[b]	PhCHO **4d**	 **5g**: 54%
8	 **3g**[c]	PhCHO **4d**	 **5h**: 75%
9	**3g**[c]	 **4e**	 **5i**: 63%
10	**3g**[c]	 **4b**	 **5j**: 71%[e]
11	 **3h**[c]	PhCHO **4d**	 **5k**: 63%
12	 **3i**[c]	PhCOCl **4c**	 **5l**: 68%[f]
13	 **3j**[c]	PhCHO **4d**	 **5m**: 64%

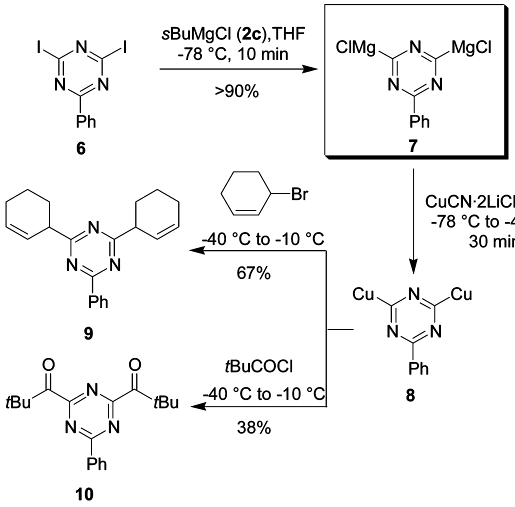
[a] Isolated yield of analytically pure product. [b] Obtained after I/Mg exchange with BuMgCl (**2a**; −78 °C, 10 min). [c] Obtained after I/Mg- exchange with OctMgBr (**2b**; −78 °C, 10 min). [d] Obtained after transmetalation with $ZnBr_2 \cdot LiCl$ (1.1 equiv) and subsequent Negishi cross-coupling[13] with ethyl 4-iodobenzoate in the presence of $Pd(dba)_2$ (5 mol %) and tfp (10 mol %). [e] Obtained after addition of $CuCN \cdot 2LiCl$ (20 mol %). [f] Obtained after transmetalation with $CuCN \cdot 2LiCl$ (1.1 equiv).

reagent **3g** afforded, after addition to PhCHO (**4d**) or *p*-NC-C_6H_4CHO (**4e**), the functionalized 1,3,5-triazinyl alcohols **5h**,**i** in 63−75% yield (entries 8 and 9). Similarly, a Cu-catalyzed allylation of **3g** provided the triazinyl-substituted acrylate **5j** in 71% yield (entry 10). The ethoxycarbonyl-, bromo-, and cyano-substituted triazinylmagnesium reagents **3h**−**j** underwent similar additions to PhCHO (**4d**) or Cu-mediated benzoylation with PhCOCl (**4c**), leading to trisubstituted 1,3,5-triazine derivatives **5k**−**m** in 63−68% yield (entries 11−13).

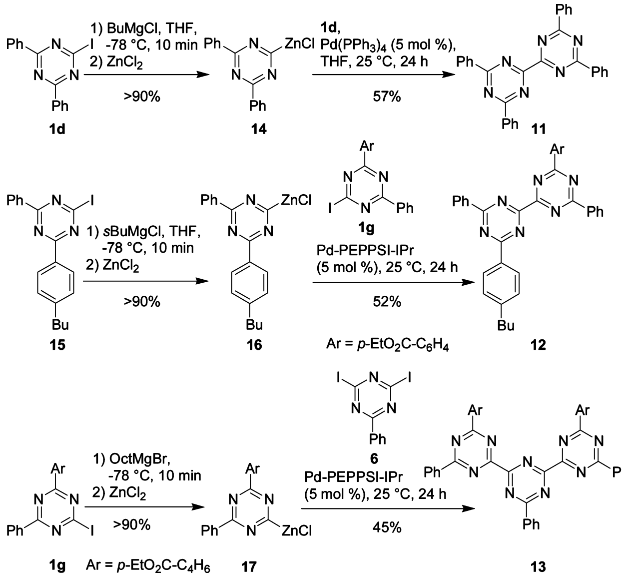
In general, the preparation of bis-magnesiated aromatics requires harsh reaction conditions, and only a few examples have been reported.[17] However, the I/Mg exchange of 2,4-diiodo-1,3,5-triazine (**6**) with *s*BuMgCl (**2c**; 2.2 equiv, −78 °C, 10 min) readily furnished the doubly magnesiated 1,3,5-triazine **7** (>90% yield[18]).

Transmetalation of **7** with CuCN·2LiCl (2.2 equiv, −78 to −40 °C) afforded the biscopper derivatives which after allylation or acylation produced the bis-functionalized triazines **9** and **10** in yields of 67% and 38%, respectively (Scheme 2). Conjugated molecules bearing 1,3,5-triazine moieties may exhibit useful opto-electronic properties.[19] We have used the functionalized triazinylmagnesium reagents of type **3** for the syntheses of trimeric and dimeric derivatives **11**−**13** (Scheme 3). Thus, 2-iodo-4,6-diphenyl-1,3,5-triazine (**1d**) undergoes a smooth I/Mg exchange with BuMgCl (**2a**; 1.1 equiv, −78 °C, 10 min) and leads after a transmetalation with ZnCl$_2$ (1.05 equiv, −78 °C, 10 min) to the corresponding 1,3,5-triazinylzinc chloride **14** (>90% yield[18]). Subsequent Pd(0)-catalyzed cross-coupling[13] with the iodotriazine **1d** (1.0 equiv, −78 to 25 °C, 24 h) provided the dimeric triazine **11** in 57% yield (Scheme 3). Similarly, the I/Mg exchange reaction of 2-iodo-4-(4-butylphenyl)-6-phenyl-1,3,5-triazine (**15**) with *s*BuMgCl (**2c**; 1.1 equiv, −78 °C, 10 min) followed by ZnCl$_2$ addition furnished the 1,3,5-triazinylzinc reagent **16**. Subsequent Negishi cross-coupling[13] with **1g** (1.0 equiv) using Pd-PEPPSI-IPr[20] (5 mol %, 25 °C, 24 h) led to the dimeric triazine **12** in 52% yield (Scheme 3).

Scheme 2. Preparation of the Dimagnesiated 1,3,5-Triazine Derivatives **9** and **10**



Scheme 3. Preparation of Dimeric and Trimeric Triazines **11**−**13**



The trimeric triazine derivative **13** was prepared from the iodotriazine **1g** by I/Mg exchange and transmetalation with ZnCl$_2$, leading to the zinc reagent **17** (>90% yield[18]). Negishi cross-coupling of **17** with 2,4-diiodo-6-phenyl-1,3,5-triazine (**6**) in the presence of Pd-PEPPSI-IPr[20] (5 mol %, 25 °C, 24 h) affords the triazine **13** in 45% yield (Scheme 3).

In summary, we have developed a new method for the preparation of stable mono- and bis(1,3,5-triazinyl)magnesium reagents, which react with aldehydes, acid clorides, and allylic halides, furnishing a wide range of new functionalized fully substituted 1,3,5-triazine derivatives. Remarkably, dimeric and trimeric triazine derivatives were also prepared using triazinylzincs as key intermediates. Further investigations of these reagents and functionalized, fully substituted products, especially toward applications as opto-electronic materials, are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and characterization data of all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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